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Studies on the asymmetric synthesis of huperzine A. Part 2: Highly enantioselective palladium-catalyzed bicycloannulation of the β-keto-ester using new chiral ferrocenylphosphine ligands

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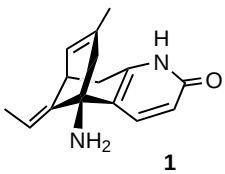
Abstract—New chiral ferrocenylphosphine ligands were designed and tested in the enantioselective bicycloannulation of β-keto-ester **2** with bifunctional allylic agent **4**. A range of e.e. values from 80 to 90% of the bicyclic intermediate **6** was achieved. Subsequently, enantiopure (−)-huperzine A was prepared in ca. 40% yield from β-keto-ester **2**.

(−)-Huperzine A (Hup A, **1**), a Lycopodium alkaloid isolated from Chinese herb *Huperzia serrata*, is a potent reversible acetylcholinesterase inhibitor.[1–3] Hup A has recently been approved as a new drug for the treatment of Alzheimer's disease in China.



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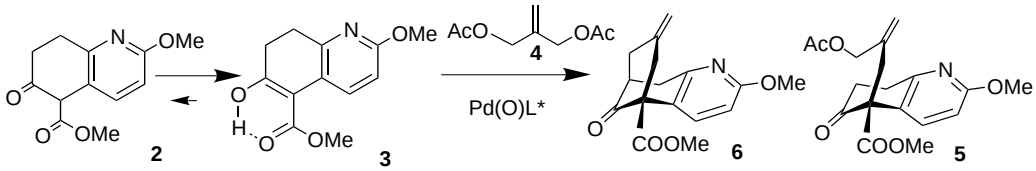
After completing the synthesis of (±)-**1**,[4,5] several groups have devoted their efforts to perform various asymmetric syntheses by means of chiral auxiliary and catalyst in stereoselective Michael reaction of β-keto-ester **2** with methacrolein,[6] and stereoselective palladium-catalyzed bicycloannulation of β-keto-ester **2** with 2-methylene-1,3-propanediol diacetate **4**.[7]

To create a quaternary stereogenic carbon center on prochiral nucleophile **2**, followed by bicycloannulation, represents a unique challenge for the stereoselective synthesis of (−)-**1**.

Based on our experience and knowledge in asymmetric synthesis of (−)-**1** and taking account of practical and efficient operation, we have focused our attention on the enantioselective palladium-catalyzed bicycloannulation of β-keto-ester **2**, which usually exists as an achiral form **3** as shown in Scheme 1.

We now report herein our recent results by using new chiral ligands for the enantioselective bicycloannulation. Bicyclic product **6** was obtained in good yield and with e.e. of 80–90%. Consequently, the total synthesis of (−)-**1** was accomplished in high yield.

According to the reaction mechanism, the stabilized nucleophile resides distal to the chiral ligand in the



Scheme 1.

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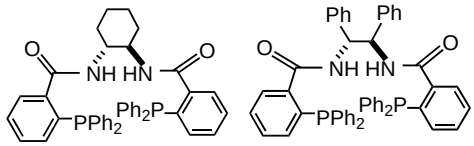
transition state, so that early asymmetric palladium-catalyzed allylation of β-keto-esters usually occurred with low stereoselectivity.[8] Recently, stereoselectivities of up to 99% e.e. have been achieved in the allylic alkylation of β-keto-esters such as 1-tetralone-2-carboxylates by use of the chiral ligand **7** introduced by Trost's group.[9]

Therefore, we attempted to conduct the enantioselective bicycloannulation, utilizing chiral ligand **7** in toluene, the yield and e.e. value of the desired product **6** was poor and the major product was intermediate **5** (entry 1).



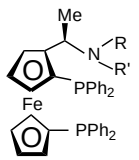
7 **8**

Chiral ligand **8**[10] was also tested and almost the same result was given (entry 2). The results are summarized in Table 1. However, Terashima's group reported that no product formed in the bicycloannulation with ligand **7** and **8** in 1,4-dioxane.[11] It seems that a chiral ligand only suits certain substrates for asymmetric allylation and therefore, it was necessary for us to seek suitable chiral ligands for matching with the β-keto-ester nucleophile, **2**.

Hayashi et al. developed chiral ferrocenylphosphine ligands having a hydroxyl group at the terminal of tether chain and used them for palladium-catalyzed asymmetric allylation of active methine compounds.[12] It is known that the length of the side chain bearing the terminal hydroxyl group at the nitrogen of ferrocenylphosphine ligands might play a very crucial role explained as *secondary ligand–substrate interaction*,[13] involving a hydrogen bond between the hydroxyl group of the ligand and the reacting nucleophile.

Terashima's group first reported palladium-catalyzed enantioselective bicycloannulation of β-keto-ester **2** in 64% e.e. utilizing chiral ligand **9**, tethering a four carbon chain with terminal hydroxyl group.[7a] In a previous paper,[14] we reported that some chiral ferrocenylphosphine ligands were examined in the enantioselective bicycloannulation and e.e. values of up to 52% were obtained.

We were encouraged by the promising results mentioned above and thus prepared a number of new chiral ferrocenylphosphine ligands by the known procedures.[12] The enantioselectivity of the bicycloannulation in Scheme 1 was evidently improved by using ligand **10** (81% e.e., entry 3), in which the *N*-methyl group of ligand **9** was replaced by an *N*-ethyl group. The e.e.



9 R=CH_3, R=$(CH_2)_4OH$
10 R=C_2H_5, R'=$(CH_2)_4OH$
11 R=i-Pr, R'=$(CH_2)_4OH$
12 R=Bn, R'=$(CH_2)_4OH$
13 R=Bn, R'=$(CH_2)_3C(CH_3)_2OH$
14 R=H, R'=$(CH_2)_4OH$
15 R=CH_3, R=$(CH_2)_5OH$
16 R=C_2H_5, R'=$(CH_2)_5OH$
17 R=i-Pr, R'=$(CH_2)_5OH$
18 R=cyclopentyl, R'=$(CH_2)_5OH$
19 R=cyclohexyl, R'=$(CH_2)_5OH$

Table 1. Enantioselective palladium-catalyzed bicycloannulation of β-keto-ester **2** with bifunctional allylic agent by various chiral ligands[a]

Entry	Ligand	Solvent	Base	Bifunctional allylic agent	Yield (%) **6**[b]	E.e. (%)[c]	Remarks
1	**7**	Toluene	TMG	**4**	12.9	6	**5** 64%
2	**8**	Toluene	TMG	**4**	15.5	8	**5** 59%
3	**10**	Toluene	TMG	**4**	98.3	81	
4	**11**	CH_2Cl_2	DBU	**4**	77.4	56	
5	**12**	CH_2Cl_2	DBU	**4**	90.6	44	
6	**13**	CH_2Cl_2	DBU	**4**	82.4	32	
7	**14**	Toluene	TMG	**4**	60.6	40	
8	**16**	Toluene	TMG	**4**	97.0	66	
9	**17**	Toluene	TMG	**4**	80.0	71	
10	**18**	Toluene	TMG	**4**	82.0	90.3	[d]
11	**19**	Toluene	TMG	**4**	98.0	65	
12	**10**	Toluene	TMG	**20**	45.9	39	[e]
13	**18**	Toluene	TMG	**21**	66.0	82	
14	**10**	Toluene	TMG	**21**	96.8	70	

[a] The experiments were generally performed as follows: Under nitrogen, 0.010 mmol of (η^3-C_3H_5)PdCl dimer, chiral ligand (0.022 mmol) and allylic agent (0.25 mmol) were dissolved in solvent (4 ml), the mixture was stirred at rt for 1 h and then added to the mixture of β-keto-ester **2** (0.20 mmol) and base (0.50 mmol) in the same solvent (4 ml) at −25 to −20°C. The reaction was maintained at this temperature for 24 h. Besides the product **6**, sometimes intermediate **5** was observed by TLC, and the bicycloannulation was then completed by raising temperature to rt for an additional 24 h.

[b] Isolated yield purified by preparative TLC.

[c] The e.e. values were determined by ^{1}H NMR in the presence of chiral shift reagent Eu(hfc)$_3$.

[d] The e.e. value was checked by HPLC in Chiralcel OD column.

[e] The reaction proceeded at −78°C overnight and then the temperature was allowed to rise slowly to rt.

values of product **6** were reduced by ligands **11**, **12** and **13** (entries 4–6), which have a larger alkyl group at nitrogen or methyl groups in the chain. For further observing the influence of the substituent at nitrogen upon the enantioselectivity of the bicycloannulation, ligand **14**, a secondary amine, was prepared and tested, only 40% e.e. of product **6** was obtained (entry 7).

It is obvious that fine-tuning of the size of the *N*-substituent of the ligand with an appropriate chain length has a dramatic effect on the enantioselectivity of the bicycloannulation.

According to Terashima's report,[7a] the enantioselectivity was lower (35% e.e.) using ligand **15** with a five methylene chain. We prepared several new ligands **16**, **17**, **18** and **19** with a bigger substituent than methyl at nitrogen. Chiral ligands with ethyl or *iso*-propyl groups induced moderate enantioselectivity (entries 8 and 9). Surprisingly, a 90.3% e.e. of product **6** was achieved using ligand **18** with a cyclopentyl group at nitrogen (entry 10), but the e.e. value decreased to 65% when ligand **19** was used (entry 11), in which a cyclohexyl group replaced the cyclopentyl group.

In order to optimize the e.e. values and chemical yield of the bicycloannulation product **6**, besides diacetate **4**, other bifunctional allylating agents, such as **20**, **21** and **22** were also prepared and examined.

20 **21** R=Bz **22** R=CF_3CO

The allylic chloride is more reactive towards Pd(0) than corresponding acetate.[15] Utilizing chloride **20**, the bicycloannulation was performed in −78°C, but both the enantioselectivity and chemical yield were low (entry 12). It is possible that in the presence of base, nucleophilic substitution of β-keto-ester **2** by the chloride competed with the palladium-catalyzed allylation. Moreover, in order to increase steric interaction, bifunctional dibenzoate **21** was tested. Regrettably, the enantioselectivity was lower than that seen with diacetate **4** (entries 13 and 14). In addition, bifunctional trifluoroacetate **22** was also tested, but no product was found. Trifluoroacetate **22** is possibly unstable in the basic reaction medium.

All experimental results for the enantioselective bicycloannulation are shown in Table 1.

With the efficient chiral ligands in hand, the chiral non-racemic product **6** was afforded by (*R*,*S*)-ferrocenylphosphine ligands such as (*R*,*S*)-**10** and **18**, in desired configuration for synthesis of (−)-**1**. Subsequently, treatment of **6** with triflic acid furnished key intermediate **23**. According to the known procedures,[11,16] the enantiopure (+)-**23**[17] was afforded after enantioenrichment by recrystallization from *n*-hexane, and through the same reaction sequence enantiopure (−)-**1** was produced in ca. 40% yield from β-keto-ester **2** as shown in Schemes 1 and 2.

The enantioselective bicycloannulation is a crucial procedure in the palladium-catalyzed asymmetric synthesis of (−)-**1**. Further studies into the fine-tuning of such chiral ferrocenylphosphine ligands are being carried out in our laboratory.

Acknowledgements

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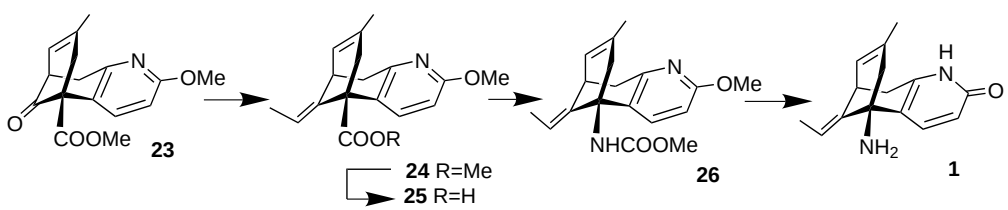

Scheme 2.

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17. (+)-**23**: $[\alpha]_D^{16} = +71.6$ (*c* 0.52, $CHCl_3$), mp 138–140°C, [Ref. 11 data reported $[\alpha]_D^{20} = +67.8$ (*c* 0.52, $CHCl_3$), mp 139–140°C].